POLITECNICO DI TORINO
Repository ISTITUZIONALE

Supramolecular Recognition Allows Remote, SiteSelective CH Oxidation of Methylenic Sites in Linear Amines

Original
Supramolecular Recognition Allows Remote, SiteSelective CH Oxidation of Methylenic Sites in Linear Amines / Giorgio, Olivo; Farinelli, Giulio; Alessia, Barbieri; Osvaldo, Lanzalunga; Stefano Di, Stefano; Miquel, Costas. - In: ANGEWANDTE CHEMIE. - ISSN 1521-3773. - Angew.Chem. Int .Ed. 2017, 56,16347 –16351:56(2017), pp. 16347-16351. [10.5517/ccdc.csd.cc1z5v88]

Availability:
This version is available at: 11583/2707872 since: 2018-05-21T11:48:52Z

Publisher:
wiley-VCH

Published
DOI:10.5517/ccdc.csd.cc1z5v88

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright
Wiley postprint/Author's Accepted Manuscript

This is the peer reviewed version of the above quoted article, which has been published in final form at http://dx.doi.org/10.5517/ccdc.csd.cc1z5v88.This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

(Article begins on next page)

12 October 2024

A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

GDCh

International Edition

www.angewandte.org

Accepted Article

Title: Supramolecular recognition allows remote, site-selective C-H oxidation of methylenic sites in linear amines

Authors: Giorgio Olivo, Giulio Farinelli, Alessia Barbieri, Osvaldo Lanzalunga, Stefano Di Stefano, and Miquel Costas

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201709280
Angew. Chem. 10.1002/ange.201709280

Link to VoR: http://dx.doi.org/10.1002/anie.201709280
http://dx.doi.org/10.1002/ange.201709280

WILEY-VCH

10.1002/anie.201709280

WILEY-VCH

COMMUNICATION

Supramolecular recognition allows remote, site-selective C-H oxidation of methylenic sites in linear amines

Giorgio Olivo,[a]* Giulio Farinelli,[b] Alessia Barbieri,[b] Osvaldo Lanzalunga,[b] Stefano Di Stefano[b]* and Miquel Costas[a]*

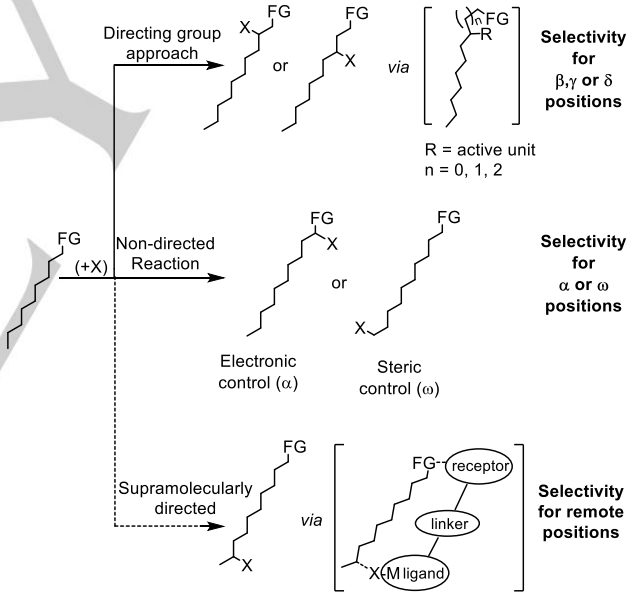
Abstract: Site-selective C-H functionalization of aliphatic alkyl chains stands as a longstanding challenge in oxidation catalysis, given the comparable relative reactivity of the different methylenes. Herein, we describe a supramolecular, bioinspired approach to address this challenge. We designed a Mn complex, able to catalyze C(sp^3)-H hydroxylation with H_2O_2, equipped with 18-benzocrown-6 ether receptors that bind ammonium substrates *via* hydrogen bonding. Reversible pre-association of protonated primary aliphatic amines with the crown ether selectively exposes remote positions (C8 and C9) to the oxidizing unit, resulting in a site-selective oxidation. Remarkably, such control of selectivity retains its efficiency for a whole series of linear amines, overriding the intrinsic reactivity of C-H bonds, no matter the chain length.

Unfolding the great potential of C-H oxidations in synthesis requires a precise and predictable control over reaction site-selectivity. Nature masters this control by precisely orienting the substrates towards the enzyme active site by means of multiple weak interactions. Conversely, artificial catalysts struggle to achieve such selectivity.[1] The problems faced are well highlighted in the selective hydroxylation of alkyl chains, a longstanding challenge in oxidation catalysis. The strength of their C-H bonds (~96 kcal mol^{-1}) coupled with the lack of appreciable differences in electronic and steric properties makes the internal methylenes practically indistinguishable (Scheme 1).[1] As a consequence, oxidation of alkyl chains affords statistical mixtures of products, only slightly affected by the use of very bulky catalysts.[2] A good selectivity can be only attained *via* intramolecular reactions, using a directing group[1a,3,4] or incorporating the reactant into the substrate[5] (Scheme 1). However, this strategy has two limitations: it cannot access C-H bonds outside a short range (β, γ or δ positions) and requires stoichiometric, preinstalled directing (or reactive) groups.[6]

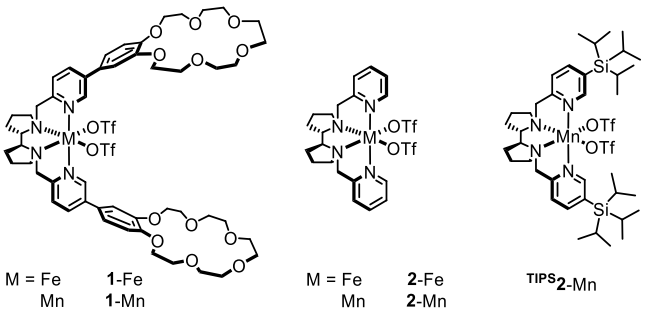
Supramolecular chemistry may offer a way past these limitations.[8,9] Reversible binding of the substrate to a receptor anchored to the catalyst can expose specific C-H bonds to the oxidizing unit, thus determining the selectivity of the hydroxylation (Scheme 1). Seminal works[10] demonstrated the feasibility of this approach, although the strict shape and size complementarity required for recognition limited the scope to few, well-crafted substrates (Figure 1).

Nevertheless, we reasoned that this approach may permit the elusive remote oxidation of alkyl chains.[1b,3b,6,11] Towards this aim, we designed catalysts **1**-Mn and **1**-Fe (Scheme 2, synthesis and characterization in the SI, pages 16-38) equipped with 18-benzocrown-6 ether (BC) receptors to bind and orient primary ammonium ions[15] (Figure 1). The catalytic center is a Mn[12] or Fe[13] PDP complex (**2**-M, Scheme 2), known to catalyze aliphatic C-H hydroxylation with H_2O_2 and acetic acid (AcOH).[14] Simple protonation of linear alkyl amines would provide optimal substrates to test our hypothesis.[16]

As anticipated, titration of **1**-Fe with protonated decylamine **3** results in a strong 1:2 binding (both $K_{ass} \geq 10^4$ M^{-1}, pages 39-43 in SI) in CD_3CN at -40°C. At this temperature the complex, that is



Scheme 1. Different approaches to the selective oxidation of alkyl chains.



Scheme 2. Catalysts used in this work.

[a] Dr. G. Olivo, Dr. M. Costas
Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química
Universitat de Girona
Campus de Montilivi, 17071 Girona, Spain
E-mail: giorgio.olivo@udg.edu, miquel.costas@udg.edu,
[b] G. Farinelli, A. Barbieri, Dr. O. Lanzalunga, Dr. S. Di Stefano
Dipartimento di Chimica and Istituto CNR di Metodologie Chimiche (IMC-CNR), Sezione Meccanismi di Reazione
Sapienza Università di Roma
P.le A. Moro 5, I-00185 Rome, Italy
E-mail: stefano.distefano@uniroma1.it

Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201709280

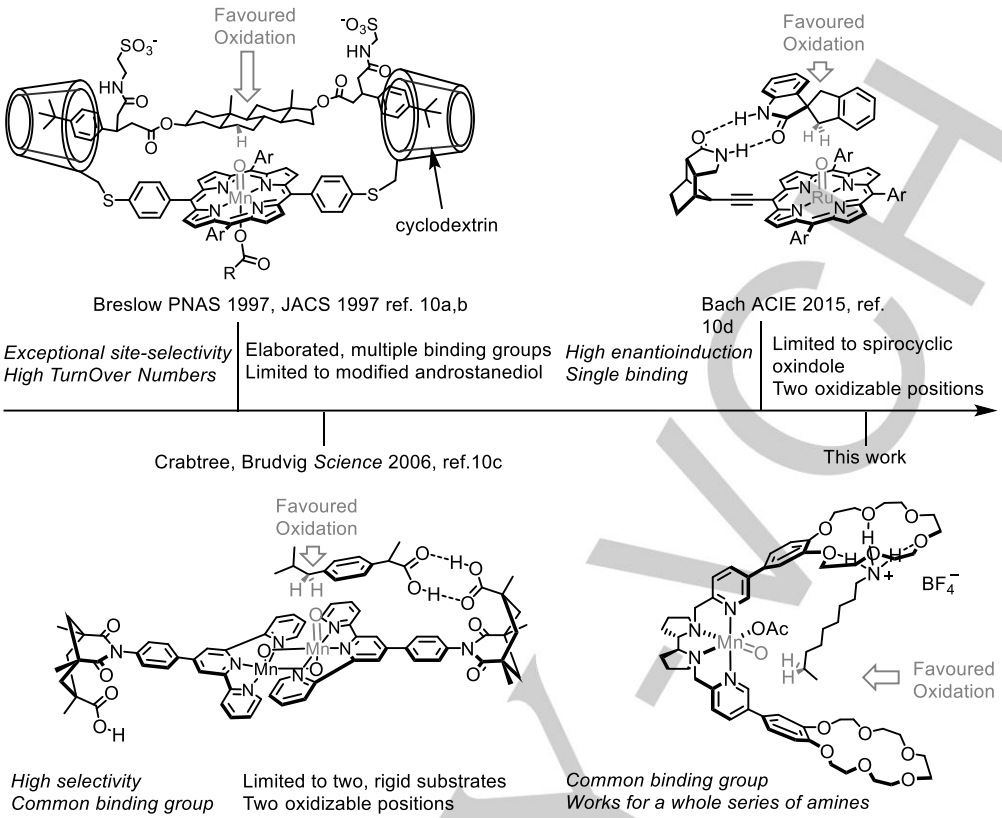


Figure 1. Supramolecularly directed C-H oxidations.

paramagnetic at 25°C, turns diamagnetic due to a temperature dependent spin crossover, enabling ^{1}H-NMR spectroscopy (see SI pages 21-22). The paramagnetism of **1**-Mn does not allow NMR titration, but mass spectrometry reveals analogous **3** binding (see SI page 44). Remarkably, the recognition tolerates the competitive hydrogen bond partners (AcOH and H_2O) required for H_2O_2 activation,[14] and is specific for primary ammonium ions (see SI pages 45-50).[15]

The electronic properties of **1**-Fe are hardly affected by the build-up of positive charge due to cation binding. Neither the Fe^{III}/Fe^{II} redox potential nor the energy of the MLCT Vis band nor the catalytic hydroxylation of **1**-Fe and **1**-Mn are significantly altered upon coordination of NH_4^+, K^+, Ca^{2+} or Ba^{2+} cations (see SI pages 78-81, 86). The only notable changes are related to the BC moiety, which becomes harder to oxidize both chemically and electrochemically (see SI pages 78, 85).

At this point, we selected decylammonium **3** as a model substrate to test our approach. Non-directed oxidation with **2**-Mn yields a mixture of ketone products (K3-K9, ketones at C3-C9, Table 1, entry 1). The first positions (up to C5) are shielded by the nearby ammonium positive charge,[16] the last positions are slightly activated due to improved sterical accessibility (C8 and C9, 53% of the total yield), and a statistical oxidation occurrs in the middle of the chain (C6, C7). To our delight, catalyst **1**-Mn substantially modified this selectivity, enhancing the selectivity for C8 and C9 positions up to 81% (entry 2).[17] A concomitant decrease (C5-C7) or suppression (C3, C4) of the oxidation on the other sites is observed. A similar, but lower, effect was also found for Fe-based complexes (entries 3 and 4).

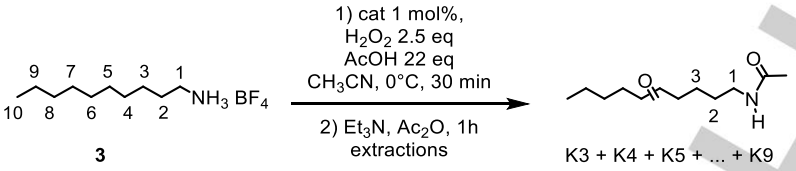
A series of control experiments were carried out to assess whether the observed change in selectivity were really due to supramolecular recognition. **i)** Addition of free BC does not modify the selectivity of the parent **2**-Mn complex, indicating that substrate binding to BC does not affect its reactivity (entries 5-7). Increasing BC loadings reduce conversion, probably because of competitive ether oxidation. **ii)** The selectivity amplification does not derive from increased steric hindrance, since the bulky catalyst ^{TIPS}**2**-Mn[18] affords the same selectivity pattern of **2**-Mn (entry 8). **iii)** Saturation of the receptor by prior coordination of $Ba(ClO_4)_2$ fully suppresses the selectivity amplification of **1**-Mn (entry 9). **iv)** Replacement of NH bonds in **3** with N-methyl ones ($DecNH_2Me^+$, $DecNHMe_2^+$) undermines the affinity of the substrate for the crown ether and yields the same selectivity pattern, no matter the catalyst used (entries 10-14). However, when there are no cationic guests that shield the BC moiety from oxidation (see SI page 85), low product yields are obtained with **1**-Mn. Consistently, addition of readily exchangeable NH_4^+ (3mol%) increases the yield (entry 14). **v)** Competitive oxidation of **3** and a neutral, more reactive substrate with methylene units (**4**) or weak tertiary C-H bonds (**5**) results in preferential hydrocarbon oxidation with **2**-Mn (Scheme 3). **1**-Mn induces a full reversal of this selectivity, which is lost upon addition of Ba^{2+} (Scheme 3). All these experiments consistently point to a recognition-driven selectivity, which overrides the intrinsic reactivity of the substrate C-H bonds.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

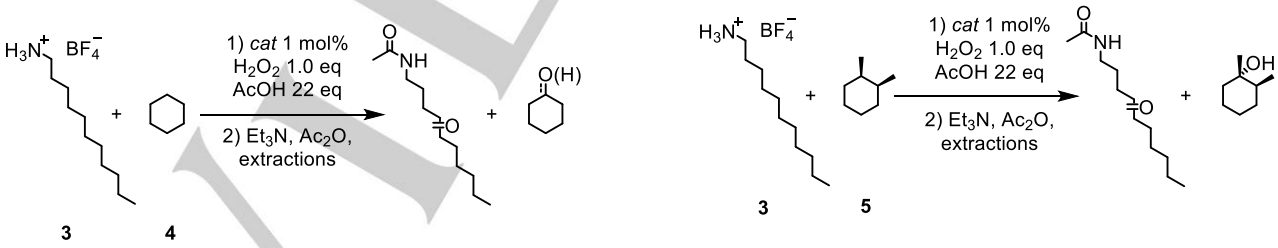
10.1002/anie.201709280

Table 1: 3 oxidation mediated by different catalysts.[a]



Entry	cat	Substrate (BF_4^- anion)	Additive mol%	Conv/ tot yield (%)	K3	K4	K5	K6	K7	K8	K9	C8 + C9 Selecti-vity[b]
1	**2**-Mn	$DecNH_3^+$(**3**)		43/34	0.5%	2%	2.5%	5.5%	5.5%	8%	10%	53%
2	**1**-Mn	"		50/36	-	-	0.5%	1.5%	5%	13%	16%	81%
3	**2**-Fe	"		48/36	-	0.5%	4%	8%	8%	7%	10%	45%
4	**1**-Fe	"		36/30	-	-	0.5%	5%	6%	6%	12%	61%
5	**2**-Mn	"	BC 2%	41/35	0.5%	1.5%	3%	6%	6%	7.5%	10%	51%
6	**2**-Mn	"	BC 10%	25/21	0.5%	1%	1.5%	3%	3%	5%	6%	54%
7	**2**-Mn	"	BC 100%	8/traces	-	-	-	-	-	-	-	
8	^{TIPS}**2**-Mn	"		62/34	traces	1%	2%	5%	8%	8%	10%	53%
9	**1**-Mn	"	Ba^{2+} 3%[c]	47/27	traces	2%	2%	5%	5%	6%	8%	58%
10	**1**-Mn	$DecNMeH_2^+$		9/7	traces	0.5%	0.5%	1.5%	1.5%	2%	2%	50%
11	**2**-Mn	"		28/26	0.5%	1%	3%	4.5%	4.5%	5%	7.5%	49%
12[d]	**1**-Mn	$DecNMe_2H^+$		11/3	traces	traces	traces	0.5%	0.5%	0.5%	0.5%	50%
13[d]	**2**-Mn	"		60/47	-	2.5%	5%	7.5%	7.5%	10%	14%	52%
14[d]	**1**-Mn	"	NH_4^+ 3%[e]	12/6	traces	0.5%	0.5%	1%	1%	1%	2%	50%

[a]Reaction conditions: cat 1 mol% (3 mol% for Fe cat.), substrate 1 eq (95 mM, 0.38 mmol), H_2O_2 2.5 eq (15 min. addition by syringe pump), AcOH 22 eq (7 eq fot Fe cat.), CH_3CN, 0°C. After 30 min., internal standard (biphenyl), Et_3N, Ac_2O and CH_2Cl_2 were added. After 1 hour, the mixture was washed with H_2O, H_2SO_4 1M, sat. $NaHCO_3$, H_2O, dried and analysed by GC. All reactions have been carried out in triplicate. Error ± 0.5%. Traces of acetylated alcohols were detected, with a selectivity pattern superimposable to that of the main ketone products. [b]Defined as (K8+K9)/tot. yield). [c]$Ba(ClO_4)_2$. [d]Different workup, see SI page 80. [e]NH_4PF_6.



cat	*Ratio (**3** Ox/**4** Ox)*	*Yield (**3** Ox)*	*Yield (**4** Ox)*
2-Mn	1 : 3.5	4%	14%
1-Mn +3%$Ba(ClO_4)_2$	1 : 4	4%	16%
1-Mn	9 : 1	18%	2%

cat	*Ratio (**3** Ox /**5** Ox)*	*Yield (**3** Ox)*	*Yield (**5** Ox)*
2-Mn	1 : 12	2.5%	30%
1-Mn +3%$Ba(ClO_4)_2$	1 : 13	2.5%	32%
1-Mn	1.3 : 1	10%	6%

Scheme 3: Competition experiments.

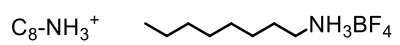
Accepted Manuscript

This article is protected by copyright. All rights reserved.

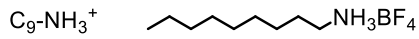
10.1002/anie.201709280

Then, we investigated the oxidation of a series of protonated, linear amines, whose chain length spans from C6 to C14, aiming at determining the precise oxidation site of **1**-Mn (Scheme 4). No oxidation occurs with short amines (C_6-NH_3^+), likely due to the strong deactivation exerted by the proximal positive charge. As the chain length increases, ketone products are formed. Catalyst **2**-Mn (Figure 2A) affords an almost statistical distribution of ketone products, except for C3-C5 (electronically deactivated) and the last two methylene units (sterically activated). Conversely, the distribution obtained with **1**-Mn (Figure 2B) reveals a bell-shaped profile, with the maximum yields on C8 and C9 sites, no matter the chain length. K10 becomes a secondary product in long-chain amines, while oxidation on positions before C8 and after C10 fade away. Such bell-shaped profile is again consistent with a supramolecular site-selectivity, with the receptor placing mainly C8 and C9 C-H bonds in the reach of the oxidizing species.

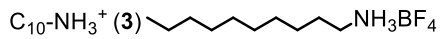
To sum up, we designed a supramolecular catalyst that oxidizes linear amines with a predictable site selectivity for C8 and C9 positions. To the best of our knowledge, this is the first report of a selective, remote C-H functionalization of alkyl chains. The key for such selectivity lies in a substrate recognition that brings these C-H bonds in the range of the active unit. Remarkably, this control of selectivity is not affected by the chain length or the presence of more (sterically) activated positions.



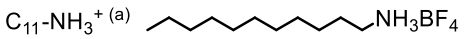
	K7	K6	K5	K4	K3
2-Mn	3%	2%	1%	0.5%	<0.5%
1-Mn	6%	2%			



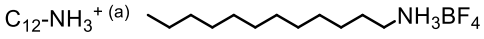
	K8	K7	K6	K5	K4	K3
2-Mn	7.5%	5%	5%	3%	1.5%	0.5%
1-Mn	11%	3.5%	1.5%			



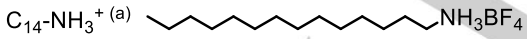
	K9	K8	K7	K6	K5	K4	K3
2-Mn	10%	8%	5.5%	5.5%	2.5%	2%	0.5%
1-Mn	16%	13%	5%	1.5%	0.5%		



	K10	K9	K8	K7	K6	K5	K4	K3
2-Mn	8%	5.5%	6.5%	6%	5%	3.5%	2%	1.5%
1-Mn	14%	18%	20%	6%	4%	1%		



	K11	K10	K9	K8	K7	K6	K5	K4	K3
2-Mn	8.5%	9%	6.5%	5.5%	4.5%	4.5%	4.5%	2.5%	1%
1-Mn	7%	9%	17%	21%	4%	3%	1%		



	K13	K12	K11	K10	K9	K8	K7	K6	K5	K4	K3
2-Mn	9%	6%	6%	7%	7%	6%	6%	4%	3.5%	2.5%	1.5%
1-Mn	1.5%	2%	3.5%	6%	19%	26%	3%	2.5%	1%		

[(a)] 15 eq. of H_2O_2, see SI page 85

Scheme 4.

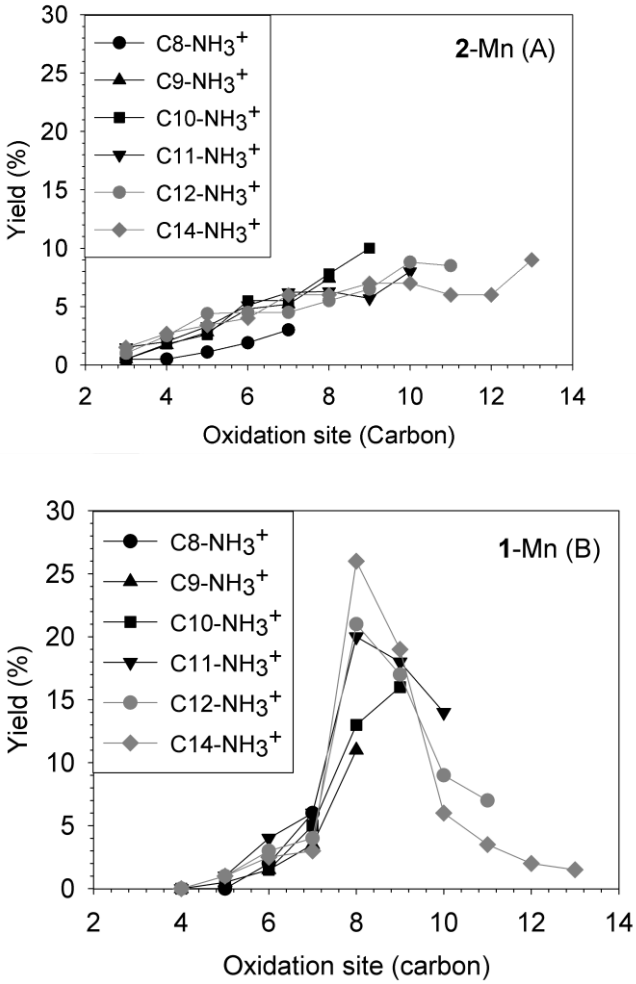


Figure 2: Distribution of oxidation products in **2**-Mn (A) and **1**-Mn (B) catalyzed oxidation of linear amines.

Acknowledgements

MC acknowledge MINECO of Spain (CTQ2015-70795-P), the Catalan DIUE (2009SGR637, ICREA Academia award) and STR of UdG for experimental support. S.D.S acknowledges MIUR, PRIN 2010CX2TLM and Sapienza Università di Roma (Ricerca Scientifica –Anno 2014). The authors thank Mr. Giorgio Capocasa for technical assistance.

Keywords: Bioinspired catalysis • Supramolecular chemistry • C-H oxidation • Regioselectivity • Molecular recognition

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201709280

[1] a) T. Brück, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2012,** *45*, 826-839; b) J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016,** *2*, 281-292; c) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011,** *50*, 3362-3374.

[2] a) M J. Nappa, C. A. Tolman, *Inorg. Chem.* **1985,** *24*, 4711-4719; b) B. R. Cook, T. J. Reinert, K. S. Suslick, *J. Am. Chem. Soc.* **1986,** *108*, 7281-7286.

[3] a) B. Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.* **2014,** *136*, 6586-6589; b) M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2012,** *134*, 9721-9726.

[4] K. Chen, J. M. Richter, P. S. Baran, *J. Am. Chem. Soc.* **2008,** *130*, 7247-7249.

[5] a) J. C. K. Chu, T. Rovis, *Nature* **2016,** *539*, 272-275; b) G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu, R. R. Knowles, *Nature* **2016,** *539*, 268-271.

[6] a) R. Breslow, M. A. Winnik, *J. Am. Chem. Soc.* **1969,** *91*, 3083-3084; b) R. Breslow, J. Rothbard, F. Herman, M. L. Rodriguez, *J. Am. Chem. Soc.* **1978,** *100*, 1213-1218.

[7] a) D. H. Sherman, S. Li, L. V. Yermalitskaya, Y. Kim, J. A. Smith, M. R. Waterman, L. M. Podust, *J. Biol. Chem.* **2006,** *281*, 26289-26297; b) S. Negretti, A. R. H. Narayan, K. C. Chiou, P. M. Kells, J. L. Stachowski, D. A. Hansen, L. M. Podust, J. Montgomery, D. H. Sherman, *J. Am. Chem. Soc.* **2014,** *136*, 4901-4904.

[8] a) P. Dydio, J. N. H. Reek, *Chem. Sci.* **2014,** *5*, 2135-2145; b) H. J. Davis, R. J. Phipps, *Chem. Sci.* **2017,** *8*, 864-877.

[9] Selected examples of recognition-driven C-H borylation: a) Y. Kuninobu; H. Ida; M. Nishi; M. Kanai, *Nat. Chem.* **2015,** *7*, 712-717; d) H. J. Davis; M. T. Mihai; R. J. Phipps, *J. Am. Chem. Soc.* **2016,** *138*, 12759-12762. Selected examples of recognition-driven olefin functionalization: c) P. Thordarson, E. J. A. Bijsterveld, A. E. Rowan, R. J. M. Nolte, *Nature* **2003**, *424*, 915-918; d) T. Šmejkal,B. Breit, *Angew. Chem. Int. Ed.* **2008**, 47, 311-315. e) P. Dydio, W. I. Dzik, M. Lutz, B. de Bruin, J. H. Reek, *Angew. Chem. Int. Ed.* **2011**, 50, 396-400. f) S. Korom, P. Ballester, *J. Am. Chem. Soc.* **2017**, *139*, 12109-12112.

[10] a) Breslow, R.; Huang, Y.; Zhang, X.; Yang, J., *Proc. Nat. Ac. Sci. USA* **1997,** *94*, 11156-11158; b) Breslow, R.; Zhang, X.; Huang, Y., *J. Am. Chem. Soc.* **1997,** *119*, 4535-4536. c) S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig, *Science* **2006,** *312*, 1941-1943. d) J. R. Frost, S. M. Huber, S. Breitenlechner, C. Bannwarth, T. Bach, *Angew. Chem. Int. Ed.* **2015,** *54*, 691-695.

[11] a) M. S. Chen, M. C. White, *Science* **2010,** *327*, 566-571; b) G. Asensio, M. E. Gonzalez-Nunez, C. B. Bernardini, R. Mello, W. Adam, *J. Am. Chem. Soc.* **1993,** *115*, 7250-7253.

[12] R. V. Ottenbacher, D. G. Samsonenko, E. P. Talsi, K. P. Bryliakov, *Org.Lett.* **2012,** *14*, 4310-4313.

[13] M. S. Chen, M. C. White, *Science* **2007,** *318*, 783-787.

[14] a) W. N. Oloo, L. Que, Jr., *Acc. Chem. Res.* **2015,** *48*, 2612-2621; b) G. Olivo, O. Cussó, M. Costas, *Chem. – As. J.* **2016,** *11*, 3148-3158.

[15] R. M. Izatt, K. Pawlak, J. S. Bradshaw, R. L. Bruening, *Chem. Rev.* **1991,** *91*, 1721-2085.

[16] a) M. Lee, M. S. Sanford, *J. Am. Chem. Soc.* **2015,** *137*, 12796-12799; b) J. M. Howell, K. Feng, J. R. Clark, L. J. Trzepkowski, M. C. White, *J. Am. Chem. Soc.* **2015,** *137*, 14590-14593.

[17] **1**-Mn does not distinguish between C8 and C9, probably for a residual flexibility of the substrate-catalyst adduct.

[18] M. Milan, M. Bietti, M. Costas, *ACS Cent. Sci.* **2017,** *3*, 196-204.

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.

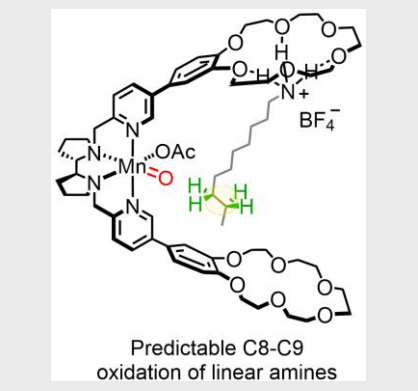
10.1002/anie.201709280

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

Supramolecular C-H oxidation: Supramolecular recognition of protonated primary amines on 18-crown-6 receptors exposes specific, remote methylenes to the Mn active site. Linear alkyl chains can thus be selectively oxidized on C8 and C9 positions with H_2O_2, overriding the intrinsic reactivity of C-H bonds.



Giorgio Olivo, Giulio Farinelli, Alessia Barbieri, Osvaldo Lanzalunga, Stefano Di Stefano* and Miquel Costas**

Page No. – Page No.

Supramolecular recognition allows remote, site-selective C-H oxidation of methylenic sites in linear amines

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.